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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/194,053	11/23/1998	MOHAMED CHOKRI	USB96AKIDM	2743

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EXAMINER	
EWOLDT, GERALD R	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/194,053	CHOKRI ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/7/04, 5/14/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44,46,47,49-51,53-55,60,61 and 88-90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44,46,47,49-51,53-55,60,61 and 88-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendments and remarks 5/14/04 have been entered.

2. Claims 44, 46, 47, 49-51, 53-55, 60, 61, 88, and newly added Claims 89 and 90 are pending.

3. In view of Applicant's Amendments and Remarks, filed 5/14/04, the previous rejections under the second paragraph of 35 U.S.C. 112 have been withdrawn.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 44, 46, 47, 49-51, 53-55, 60, 61, 88, and newly added Claims 89 and 90, stand/are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record as set forth in the paper mailed 7/29/02 and maintained in the paper mailed 5/07/03.

Briefly, the instant invention is drawn to a previously undescribed type of antigen presenting cell that possesses properties of both macrophages, i.e., phagocytic capacity, and dendritic cells, i.e., superior antigen presentation. Given the unexpected nature of the cell of the instant claims, said cell must be considered highly unpredictable. As such, an enabling specification would require significant guidance and direction, and/or working examples. The specification, however, fails to adequately disclose to one of skill in the art how to make the invention of the instant claims as broadly claimed, or even that the MD-APCs of the instant claims indeed exist as a single, specific, cell type.

The specification discloses that the MD-APCs of the instant claims are produced by a method of culturing monocytes in a medium comprising GM-CSF, cimetidine, and histamine and are characterized as being positive for surface antigens CD14, CD64, CD80 and CD86, and devoid of surface antigens CD1a, CD1c and CD83, as determined by immunofluorescence staining and flow cytometry analysis. It is noted that the specification discloses no immunofluorescence staining and flow cytometry analysis data, but merely discloses Applicant's analysis of uncontrolled data as set forth in Tables 1-5. It is the Examiner's position that the cells of the instant claims are much more likely to comprise a mixed cell culture of dendritic cells and macrophages than they are to comprise a single new, and previously undescribed, cell type. This is the Examiner's position particularly in view of the disclosure at page 5 that only 10% of the claimed cells need express CD14, only 10% of the claimed cells need express CD64, only 30% of the claimed cells need express CD80, and only 30% of the claimed cells need express CD86, a description that most certainly describes a mixed cell population.

Applicant's arguments, filed 5/14/04, have been fully considered but they are not persuasive. Applicant again argues that previously cited references, Boyer et al. (1999) and Chaperot et al. (2000), support the MD-APCs of the instant claims.

It is again noted, that neither the methods nor the cells of the references are the methods or the cells of the instant specification and claims. Regarding Boyer et al., the reference fails to teach the culture method of the instant specification, but more importantly the reference fails to teach the cells of the instant claims. As set forth in the specification and reiterated above, the cells of the instant claims are CD1a+, CD80+ and CD86+, the cells MAK cells Boyer et al. express CD86 at a lower level and intensity, are essentially devoid of CD80, and only 34% of the cells express CD1a. Additionally, the cells of the instant claims are highly phagocytotic whereas the MAK cells of Boyer et al. are not. Note, it is somewhat unclear whether Applicant is trying to argue that the MAK cells (macrophages) or the MAC-DC cells (dendritic cells) of Boyer et al. are the MD-APC cells of the instant claims. Applicant argues that the reference shows highly phagocytotic cells but those are the MAC-DC dendritic cells of the reference that are CD1a+. Either way, it is clear that neither of the cells of Boyer et al. are the cells of the instant claims.

Regarding the methods and cells of Chaperot et al., the macrophages of the reference are produced by the well-known method of culturing monocytes in GM-CSF while the dendritic cells of the reference are produced by the equally well-known method of culturing monocytes in GM-CSF and IL-13. Applicant appears to be arguing that the dendritic cells of the reference are the MD-APC cells of the instant claims. Were this argument to be persuasive, an art rejection under 35 U.S.C. 102(b) would be required (see for example, Piemonti, 1995, IDS). It is clear, however, that the dendritic cells of the reference are not the cells of the instant claims given the teaching that the DCs of the reference are CD14- and CD64-, and the majority are CD1a+.

Applicant argues that the methods of the '756 patent and Paul's *Fundamental Immunology* should not be compared to the method of the instant specification as the '756 patent does not teach the separation of adherent from nonadherent cells and Paul teaches the inclusion if IL-4 in the culture.

It is the Examiner's position that Applicant is arguing unclaimed limitations, which are particularly relevant because the claimed product is a product-by-process. None of the claims require a separation step and only new Claim 90 excludes the use of IL-4 in the cell culture. Accordingly, the argument is not found persuasive.

Applicant continues with an argument regarding the written description requirement, i.e., "..upon reviewing the present disclosure, it is clear that applicants describe new antigen-presenting cells, a process for preparing the same cellular vaccines".

Applicant is advised that the rejection was made for lack of enablement. Arguments regarding rejections for lack of adequate written description, rejections that have not been made, are not persuasive in this context.

Applicant argues, "While the Official Action contends that the description is inadequate to access the value of the asserted experiments, applicants, applicants [sic] note that the Official Action fails to provide any evidence or substantiated reasoning that challenges the validity of the date [sic] or applicants' interpretation of the date [sic] set forth in the application".

Contrary to Applicant's assertions, the previous two actions provide sufficient "evidence or substantiated reasoning" regarding the instant rejection for lack of enablement. In

particular, it has been noted that Applicant has chosen in most instances not to provide actual data, but rather Applicant has chosen to provide Applicant's interpretation of asserted data in the form of tables. Even when what appears to be data is actually disclosed, it is often difficult to interpret. For example, Table 1 indicates "Yield (% of cells) differentiated in culture", which at first glance would appear to be actual data. However, the specification fails to disclose precisely what the yield is how it is calculated. What type of cells? % in relation to what? All starting cells? The % of total viable cells at the disclosed time points? The vague and imprecise conclusion that, "there is a recovery of a large quantity of MD-APCS after 5 to 11 days of culture" is not found to be a particularly convincing argument that the MD-APC cells of the instant claims exist as a discrete cell type rather than a heterogeneous population of monocytes, macrophages, immature dendritic cells and mature dendritic cells.

Applicant argues, "Contrary the assertions the Official Action, applicants attempt to describe the experiments "after-the-fact" do not comprise an attempt introduce new matter specification. Rather, applicants' explanations of the data and table [sic] are only provided to help explain how one of ordinary skill in the art would interpret the present disclosure. As a result, applicants believe that it is improper for the Examiner not to consider applicants' explanation."

It is the Examiner's position that an opinion of how one of ordinary skill in the art would interpret the instant disclosure is the purview of experts in the field and not attorneys. Accordingly, the attorney's opinion is not found to be convincing.

Applicant argues, "the Official Action fails to provide any evidence that would suggest that the breadth of the claims was inappropriate or that the present disclosure fails to satisfy the requirements of 35 U.S.C. §112".

Applicant's assertion is simply untrue, the Examiner has cited several references, such as the '756 patent and *Fundamental Immunology*, as well as indicating how Applicant's references, such as Boyer et al. and Chaperot et al., all of which support the Examiner's position that Applicant's invention is most likely a heterogeneous population of known cell types. As Applicant has claimed a new, undescribed, and previously unknown cell type, it is incumbent upon Applicant to provide sufficient evidence that said cell type exists and is not just a heterogeneous population

of known cells. Further regarding the breadth of the claims, the specification provides just a single method comprising a single combination of reagents for producing the single asserted cell type of the instant claims. It is noted that even though the product is claimed as a product-by-process, none of the claims recite all of the disclosed method limitations (such as culture in GM-CSF, cimetidine, and histidine) nor all of the product limitations (such as a cell positive for surface antigens CD14, CD64, CD80 and CD86, and devoid of surface antigens CD1a, CD1c and CD 83). Thus, it remains the Examiner's position that the limited disclosure cannot support the product as broadly claimed.

Applicant directs the Examiner's attention to new Claim 89.

As set forth previously, the prior art is clear in teaching that the culture of a monocyte with GM-CFS (as set forth in the examples of the specification) and IL-13 will result in a dendritic cell and not the cells of the instant claims. It is unclear precisely what the culture of a monocyte in GM-CSF cimetidine, and histidine (the method actually set forth in the examples of the specification) will result in.

6. The following are new grounds of rejection.

7. Claims 44, 46, 47, 49-51, 53-55, 60, 61, 88, and newly added Claims 89 and 90 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) Monocyte-derived antigen- presenting cells (MD-APCS) having been produced by differentiating blood monocytes in vitro, in the presence of lymphocytes, GM-CSF and at least one ligand having a receptor on the surface of monocytes, <u>said MD-APCS having, when compared with monocyte derived macrophages prepared in the presence of GM-CSF only, higher phagocytic properties of formalin fixed yeast and higher ability for stimulation of allogenic T lymphocytes</u>, in Claim 44.

B) Monocyte-derived antigen-presenting cells (MD-APCS) which present the following properties: the presence on the MD-APC cell surface of surface antigens CD80 and CD86; and the presence on the MD-APC cell surface of surface antigen CD14, said MD-APCS have been produced by differentiating blood monocytes in vitro,

in the presence of lymphocytes, GM-CSF and at least one ligand having receptor on the surface of monocytes, said MD-APCS having, when compared with monocyte derived macrophages prepared in the presence of GM-CSF only, higher phagocytic properties of formalin fixed yeast and higher ability for stimulation allogenic T lymphocytes, in Claim 55.

C) An ex vivo cellular composition containing monocyte-derived antigen-presenting cells (MD-APCS) having been produced by differentiating blood monocytes vitro, in the presence of lymphocytes, GM-CSF and at least one ligand having receptor on the surface of monocytes, said cellular composition having, when compared cellular composition containing monocyte derived macrophages prepared in presence GM-CSF only, higher phagocytic properties of formalin fixed yeast and higher ability for stimulation of allogenic T lymphocytes, in Claim 88.

D) The monocyte-derived antigen-presenting cell (MD-APCS) according to claim wherein said at least ligand having a receptor on the surface of monocytes is selected from the group consisting of cimetidine and histamine, and IL-13, in Claim 89.

E) A monocyte-derived antigen-presenting cell (MD-APCS) having been produced by differentiating blood monocytes in vitro in a culture medium, in the presence of lymphocytes, GM-CSF and at least one ligand having a receptor on the surface of monocytes, said MD-APCS having when compared with monocyte-derived macrophages prepared in the presence of GM-CSF only, having higher phagocytic properties of formalin fixed yeast and higher ability for stimulation of allogenic T lymphocytes, wherein the culture medium comprises cimetidine and histamine and does not contain IL-4, IL-10, and TNF, in Claim 90.

Upon careful review of the specification no support has been found for the broadening of the instant invention, i.e., 1) the cells of the instant claims "having when compared with monocyte-derived macrophages prepared in the presence of GM-CSF only, higher phagocytic properties of formalin fixed yeast and higher ability for stimulation of allogenic T lymphocytes" or 2) the use of IL-13 as set forth in Claim 89. These limitations are disclosed only in specific examples. Such disclosures are not sufficient written description for the invention of the generic claims.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 14-22 and 27-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, specifically:

A) In Claim 47, "phagocytic capacity" has no antecedent basis in Claim 44.

B) In Claim 89, "at least ligand" would more properly be "at least one ligand".

C) In Claim 90, line 7 "having higher" would more properly be "higher".

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

12. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). Inquiries of a general nature may also be directed to the Technology Center 1600 Receptionist at (571) 272-1600.

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